18. (Amended) The method of claim 1 wherein said morphogenic protein or analog is administered at least 72 hours after the creation of said defect.

19. (Amended) The method of claims 1 or 3 wherein said morphogenic protein or analog is administered to said mammal after the initiation of fibrosis at said defect locus.

20. (Amended) The method of claims 1 or 3 wherein said morphogenic protein or analog is administered in aqueous solution.

REMARKS

The present invention is directed to a method for evaluating the activity and dosage of a candidate morpohgenic protein systemically administered at a site other than the site of a local permissive defect which has been created for evaluation purposes. The local defect can be created by, for instance, implantation of a matrix material at the site, inducing a fracture in a bone, or inducing a tear in the cartilage. See pages 9 and 10 of the present specification. The result of the candidate evaluation is compared to a control to determine the efficacy of the candidate. See examples 1-3 in the specification. The claims have been amended to reflect these distinguishing features of the present invention. Antecedent support is found on the indicated pages of the specification.

In the Office Action of January 30, 2001, the prior restriction requirement was made final as to claims 1-5 and 8-28 (currently under examination), and claims 6, 7 and 29-122 were withdrawn from consideration. Applicant notes that the election of species with respect to the morphogen (OP-1) has been withdrawn, but the election of species with respect to neural tissue has been retained. Applicant assumes that allowance of this application with respect to one elected species will result in the allowance of the generic claim encompassing that species without the necessity of additional examination of the non-elected species on the merits.

The additional, underlined space on page 3 of the specification has been deleted, and a clean copy of the revised specification showing the changes is attached to this Amendment. No new matter has been added as a result of this amendment.

Claims 2 and 4 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of this invention. This ground of rejection is respectfully traversed.

The basis for this rejection appears to be that the provisions of claims 2 and 4 regarding the distal administration of the candidate morphogen is believed to be inconsistent with the provisions of claims 1 and 3 regarding systemic administration. Applicant respectfully submits that there is no such inconsistency. The term "distal" is used to denote a site of administration which is remote from, or not in close proximity to, the actual site of the local permissive defect. The use of the term "distal" is intended to draw a contrast with other methods wherein the administration of the morphogen is required directly at the site of the injury. See pages 3 and 4 of the instant specification. The term "systemic" is intended to denote a means of administration, not the place of administration, and encompasses, e.g. parenteral, intra peritoneal and oral routes of administration. Applicant can perceive no inconsistency between the use of these terms.

Claims 1-5, 12-14, 20 and 23-28 have been rejected under 35 U.S.C. 102(b) as obvious over Rueger et al., WO 94/03200. In addition, claims 8-11, 15-19, 21 and 22 have been rejected under 35 U.S.C. 103(a) as obvious over Reuger et al. These grounds of rejection are respectfully traversed.

The Examiner has stated that Rueger et al. teaches methods for evaluating candidate molecules in *in vivo* animal models, including the evaluation of candidates for repairing the sciatic nerve and the optic nerve. Applicant cannot agree with this interpretation of the Reuger et al. reference.

Reuger et al. teaches the use of suitable morphogens as therapeutic agents for maintaining neural pathways and for enhancing the survival of neuronal cells. In addition, the reference also discloses assays in which the efficiency of morphogens can be evaluated. In describing these assays, the Examiner points to pages 99-100 and 90-93 of the reference as supporting the rejection. However, applicant submits that a careful review of these passages would actually direct one skilled in the art away from the concept of the present invention.

Pages 99-100 of Reuger et al., which describe an *in vivo assay*, state that the damage to the nerve tissue in the animal is **genetically or environmentally induced**. This is in contrast to the present claims which specifically provide that the defect is **permissive** and is intentionally created for purposes of the evaluation.

In addition, Reuger et al. also states that the morphogen is injected "within the area of the affected neurons". See, also, page 91 of the reference which states that the "OP-1 filled tube was implanted directly into the defect site". Once again, this contrasts with the methods claimed in this invention wherein the morphogen is applied systemically at a site **distal from** the site of the defect. It is an important feature of the present invention that a successful candidate morphogen must be capable of inducing repair if applied at a site the than the site of the defect, and this feature not disclosed in the reference.

The Examiner further states that the use of the instant methods in compromised animals would also be an obvious modification of the methods described in the Reuger et al. reference. However, as pointed out above, the reference fails to teach or suggest the basic features of the present claims, and in particular, the site of administration of the morphogen, and the method of creating the defect in the test subject. Accordingly, Reuger et al. would also fail to teach or suggest the features claimed in the dependent claims of this application.

Claims 1-5 and 8-28 also stand rejected under 35 U.S.C. 103(a) as obvious over the disclosure in Wang et al., WO 95/05846. This ground of rejection is also traversed.

The Wang et al. reference is directed to the use of bone morphogenic protein for repairing defects in a mammal. Since Wang et al. is limited to a process for using bone morphogenic proteins in a treatment protocol, it is clear that the reference is not directed to a process for evaluating the morphogenic activity or optimal dose regime for **candidate** morphogens as claimed in the present application. There is no disclosure in Wang et al. that the activity of a candidate morphogen can be evaluated against a control for determination of efficacy.

Moreover, and statements to the contrary in the Office Action notwithstanding, Wang specifically directs one skilled in the art to apply the bone morphogenic protein to the site of the defect. This is the exact opposite of the present claims which require the morphogen to be applied to a site distal from the site of the created defect.

In view of the foregoing facts and reasons, this application is now believed to overcome the remaining grounds of rejection, and to be in proper condition for allowance. Accordingly, reconsideration and withdrawal of the remaining grounds of rejection remaining in this application is earnestly solicited. The Examiner is invited to contact the undersigned at the telephone number listed below if this would facilitate allowance of this application.

Respectfully submitted,

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MARKED-UP CLAIMS

1. (Amended) A method for evaluating the morphogenic activity of a candidate morphogenic protein or analog thereof, the method comprising the steps of:

(a) creating, for purposes of the evaluation, a local permissive defect site in a mammal,

(b) administering [a] said candidate morphogenic protein or analog systemically to said mammal at a site distal from the local permissive defect site, [and]

(c) measuring the ability of the candidate protein or analog to induce new tissue formation at said defect site, and

(d) comparing the ability of said candidate with the ability of a control to perform the same function.

3. (Amended) A method for evaluating an optimal dosage of a candidate morphogenic protein or analog thereof for administering to a mammal, the method comprising the steps of:

(a) creating, for purposes of the evaluation, a local permissive defect site in a mammal, [and]

(b) administering [a] said candidate morphogenic protein or analog systemically to said mammal at a site distal from the local permissive defect site,

(c) measuring the ability of the candidate protein or analog to induce new tissue formation at said defect site, and

(d) comparing the ability of said candidate with the ability of a control to perform the same function.

16. (Amended) The method of claims 1 or 3 [or 4] wherein said morphogenic protein or analog is administered at least six hours after the creation of said defect.

17. (Amended) The method of claim 1 [or 4] wherein said morphogenic protein or analog is administered at least 24 hours after the creation of said defect.

18. (Amended) The method of claim 1 [or 4] wherein said morphogenic protein or analog is administered at least 72 hours after the creation of said defect.

19. (Amended) The method of claims 1 or 3 [or 4] wherein said morphogenic protein or analog is administered to said mammal after the initiation of fibrosis at said defect locus.

20. (Amended) The method of claims 1 or 3 [or 4] wherein said morphogenic protein or analog is administered in aqueous solution.